Remarks

Claims 1, 3-5, and 7-10 were pending in the subject application. By this Amendment, claim 1 has been amended. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1, 3-5, and 7-10 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

By this Amendment, Figure 6A has been amended. The figure legend incorrectly had a black box representing 100 μM DMXB plus TC-2403. The applicant submits herewith a replacement drawing sheet containing Figures 6A and 6B. As shown in the marked-up version, the black box has been replaced with an appropriate cross-hatch box. This error and the appropriate correction are obvious from the bar graphs of Figures 6A and 6B, and paragraph 0020 at page 8, and paragraph 0065 at page 24, of the specification. The applicant respectfully submits that no new matter has been incorporated into these formal drawings.

By this Amendment, claim 1 has been amended to delete acetylcholine from the recited Markush group.

Claims 1, 3-5, and 7-10 remain rejected under 35 U.S.C. §103(a) as being obvious over Crooks *et al.* (U.S. Patent No. 5,616,707) in view of Newhouse *et al.* (*Society of Biol. Psych.*, 2001, 49:268-278). The applicant respectfully submits that the claimed invention is not obvious over the cited references.

At page 4, the Office Action states that it is not clear from the patent application that the recovery after DMXB (also known as GTS-21 or 3-[2,4-dimethoxybenzylidene]-anabaseine) plus TC-2403 (metanicotine) is greater than the additive effect of each individual compound (DMXB or metanicotine) since there is no experimental data presented on metanicotine alone. Submitted herewith for the Examiner's consideration is a Declaration under 37 C.F.R. §1.132 by Dr. Roger Papke. As explained by Dr. Papke in his Declaration, ABT-418 and DMXB produce varying amounts of residual inhibition (or protracted desensitization), making them in fact mixed agonists-antagonists, as described in paragraphs 0026 and 0027 of the patent application. Thus, while their agonist activity makes compounds such as ABT-418 and DMXB candidate drugs for CNS disorders,

their usefulness would be limited by their residual antagonist activity, which restricts their effectiveness and potentially would compromise other functions mediated by receptors in the brain and peripheral nervous system.

As Dr. Papke explains at page 15, lines 10-14, of his Declaration, Figure 3B of the patent application shows the concentration-response relationship for the recovery of control (the neurotransmitter acetylcholine (ACh)) response amplitude after application of DMXB alone at the indicated concentrations (and Figure 3B of Papke, *JPET* 301:765-773, 2002, which was submitted with the applicant's previous Amendment). ACh is the endogenous agonist for nicotinic acetylcholine receptors. Figures 3C and 3D of the application show the effect of metanicotine alone on alpha3beta4 receptors. Dr. Papke notes "as shown in Figures 3C and 3D, respectively, metanicotine produces very little activation or desensitization of these ganglionic type receptors by itself (also shown in Figures 3C and 3D of Papke, 2002, and Table 2 and Figures 2C and 2F of Papke *et al.*, *J. Neurochem.*, 75:204-216, 2000, which was submitted with the applicant's previous Amendment)".

As Dr. Papke states in his Declaration at page 15, lines 19-28, and page 16, lines 1-3:

> An unexpected finding is that co-application of metanicotine with DMXB reduces the inhibitory effects that would otherwise result from application of DMXB alone. Figure 6A shows fractional recovery of the control (acetylcholine) response when oocytes expressing wild-type alpha3beta4 receptors were treated with DMXB alone (solid white bar, far left) or in the presence of metanicotine (cross-hatch bar, far right) (also shown in Figure 6A of Papke, 2002). Only co-application of metanicotine decreased the residual inhibition measured after application of DMXB. As is evident from the graph of Figure 3D of the patent application, if the recovery of the control response for metanicotine alone were to be presented in the bar graph of Figure 6A (*e.g.*, next to DMXB alone), it would show a response of approximately 1.0, neither activating nor inhibiting the alpha3beta4 receptor. Thus, application of metanicotine does not just not inhibit the alpha3beta4 receptor, it actually protects the alpha3beta4 receptor from the residual inhibition that would otherwise occur upon application of DMXB or other mixed agonist-antagonists, such as ABT-418. This is not an additive effect.

As indicated by Dr. Papke, if graphed in Figure 6A of the application, metanicotine alone would neither activate nor inhibit the receptor. However, when co-applied with the mixed agonist-antagonist, metanicotine does not merely fail to inhibit the receptor, it actually protects the receptor from the residual inhibition of the mixed agonist-antagonist. Therefore, if DMXB were administered

for the purpose of stimulating alpha3beta4 receptors in the CNS, co-administration of metanicotine would have a synergistic activity, reducing the peripheral side effects of DMXB (or other mixed agonist-antagonists) alone. As Dr. Papke indicates at page 16, lines 4-10, of his Declaration, metanicotine has virtually no effects on alpha3beta4 receptors (Papke 2000) and "this ability of metanicotine to protect alpha3beta4 nAChR function from long-term inhibition by antagonists or mixed agonists-antagonists was not previously recognized in the scientific literature, and would not have been expected based upon the activities of metanicotine and the other compounds, individually". The observation that protection from inhibition was provided by a drug that lacks intrinsic inhibitory activity would be unexpected to those of ordinary skill in the art.

Furthermore, Dr. Papke explains in his Declaration that the surprising ability of metanicotine to protect nAChR from the inhibitory after-effects of other potentially therapeutic compounds is significant, clinically. For example, metanicotine can be co-administered with other potentially therapeutic mixed agonists-antagonists that may otherwise be disqualified for therapeutic use due to their inhibitory side effects. As Dr. Papke states in his Declaration at page 16, lines 18-22, examples of side effects that would be expected include "vasoconstriction, constipation, pupil dilation, xerostemia (dry mouth), loss of accommodation (focusing ability), urine hesitancy and retention, impotence, anorexia, eructation (belching), and orthostatic hypotension."

It is well settled in patent law that "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue" *In re Corkill*, 226 USPQ 1005 (Fed. Cir. 1985). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (*i.e.*, demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989). Furthermore, the presence of a property not possessed by the prior art is evidence of nonobviousness. *In re Papesch*, 137 USPQ 43 (C.C.P.A. 1963).

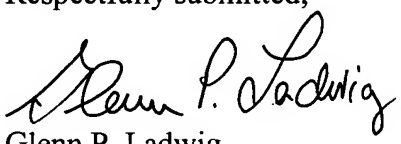
The benefits of the claimed method are unexpected in view of the prior art, and have a significant, practical advantage. Therefore, the applicant respectfully submits that the claimed invention is not obvious over the prior art. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time
Declaration by Dr. Papke under 37 C.F.R. §1.132
Replacement Drawing Sheet
Marked-up Drawing Sheet

Patent Application
Docket No. UF-293
Serial No. 10/036,988

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Brian Yong S. Kwon
Art Unit	:	1614
Applicant	:	Roger L. Papke
Serial No.	:	10/036,988
Filed	:	December 31, 2001
For	:	Compositions and Methods for Treatment of Neurological Disorders

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DECLARATION OF ROGER L. PAPKE, Ph.D., UNDER 37 C.F.R. §1.132

Sir:

I, Roger L. Papke, Ph.D., of the University of Florida, Department of Pharmacology and Therapeutics, hereby declare:

THAT, I am the named inventor on the above-referenced patent application;

THAT, I have received the following degrees:

Ph.D. Neurobiology and Behavior	1987	Cornell University, Ithaca, NY
M.S. Physiology	1976	New York University, NY, NY
B.A. Biology and Classics	1975	New York University, NY, NY

THAT, I have been employed professionally as follows:

1987	Postdoctoral Research Associate: Department of Pharmacology, Cornell University
1987	Lecturer: Department of Neurobiology and Behavior, Cornell University

1988-1993	Postdoctoral Research Fellow: Molecular Neurobiology Laboratory, Salk Institute
1993-1998	Assistant Professor: Department of Pharmacology and Therapeutics, University of Florida
1994-1998	Affiliate Assistant Professor: Department of Neuroscience University of Florida
1998-present	Associate Professor: Department of Pharmacology and Therapeutics, University of Florida
1998-present	Affiliate Associate Professor: Department of Neuroscience University of Florida

THAT, I have published extensively in my field and some of the publications are as follows:

1. Roger L. Papke and Robert E. Oswald. 1986. Effects of allosteric ligands on the gating of single channel currents in bc3h-1 cells. N.A.T.O. *Advanced Research Workshop Mechanism of Action of The Nicotinic Acetylcholine Receptor,* Santorini, Greece. NATO ASI Series Vol. H3 Ed. A. Maelicke Springer-Verlag, Berlin.

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THAT, through my years of research, I have kept up to date on the technical literature and maintained contact with experts in the field by participating in professional meetings and seminars, and by direct personal contact. As a result, I am familiar with the general level of skill of those working in the fields of molecular biology and pharmacology, and particularly as they relate to nicotinic acetylcholine receptors;

THAT, I have read and understood the specification and claims of the subject application and the Office Actions dated August 26, 2003 and February 26, 2004;

AND, being thus duly qualified, do further declare:

The Office Action dated February 26, 2004 indicates that because the Crooks *et al.* patent teaches the administration of metanicotine (also known as TC-2403, RJR-2403, or (E)-N-methyl-4-(3-pyridinyl)-3-butene-1-amine) to treat Alzheimer's disease (AD) and the Newhouse *et al.* publication teaches the administration of ABT-418 (also known as (S)-3-methyl-S-(1-methyl-2-pyrrolidinyl)isoxazole) to treat AD, it would have been obvious to combine the two therapies to treat AD with enhanced therapeutic effect. Furthermore, at page 4, the Office Action states that it is not clear from the patent application that the recovery after DMXB (also known as GTS-21 or 3-[2,4-dimethoxybenzylidene]-anabaseine) plus metanicotine is greater than the additive effect of each individual compound (DMXB or metanicotine) since there is no experimental data presented on metanicotine alone.

I wish to elaborate on the significance of the discovery that co-administration of metanicotine protects nicotinic acetylcholine receptors (nAChR) in the autonomic nervous system from side effects that would be expected from the administration of mixed agonists-antagonists alone. As explained in the patent application, numerous nicotinic compounds, such as metanicotine, ABT-418, and DMXB, have been characterized as agonists or partial agonists for select nAChR subtypes.

Additionally, with the exception of metanicotine, these compounds produce varying amounts of residual inhibition (or protracted desensitization), making them in fact mixed agonists-antagonists, as described in paragraphs 0026 and 0027 of the patent application. Thus, while their agonist activity makes compounds such as ABT-418 and DMXB candidate drugs for CNS disorders, their usefulness would be limited by their residual antagonist activity, which restricts their effectiveness and potentially would compromise other functions mediated by receptors in the brain and peripheral nervous system.

The ordinarily skilled artisan would expect peripheral side effects from the administration of DMXB (*i.e.*, blocking receptors in autonomic ganglia), based upon its residual inhibitory effects on wild-type alpha3beta4 receptors. This is demonstrated in Figure 3B of the patent application, which shows the concentration-response relationship for the recovery of control (the neurotransmitter acetylcholine (ACh)) response amplitude after application of DMXB alone at the indicated concentrations (and Figure 3B of Papke, *JPET* 301:765-773, 2002). ACh is the endogenous agonist for nicotinic acetylcholine receptors.

Figures 3C and 3D of the application show the effect of metanicotine alone on alpha3beta4 receptors. As shown in Figures 3C and 3D, respectively, metanicotine produces very little activation or desensitization of these ganglionic type receptors by itself (also shown in Figures 3C and 3D of Papke, 2002, and Table 2 and Figures 2C and 2F of Papke *et al.*, *J. Neurochem.*, 75:204-216, 2000).

An unexpected finding is that co-application of metanicotine with DMXB reduces the inhibitory effects that would otherwise result from application of DMXB alone. Figure 6A shows fractional recovery of the control (acetylcholine) response when oocytes expressing wild-type alpha3beta4 receptors were treated with DMXB alone (solid white bar, far left) or in the presence of metanicotine (cross-hatch bar, far right) (also shown in Figure 6A of Papke, 2002). Only co-application of metanicotine decreased the residual inhibition measured after application of DMXB. As is evident from the graph of Figure 3D of the patent application, if the recovery of the control response for metanicotine alone were to be presented in the bar graph of Figure 6A (*e.g.*, next to DMXB alone), it would show a response of approximately 1.0, neither activating nor inhibiting the alpha3beta4 receptor. Thus, application of metanicotine does not just not inhibit the alpha3beta4

receptor, it actually protects the alpha3beta4 receptor from the residual inhibition that would otherwise occur upon application of DMXB or other mixed agonist-antagonists, such as ABT-418. This is not an additive effect.

Thus, if DMXB were given for the purpose of stimulating alpha3beta4 receptors in the CNS, concomitant treatment with metanicotine, which has virtually no effects on brain alpha3beta4 receptors (Papke 2000), would have a synergistic activity, reducing the peripheral side effects of DMXB alone. This ability of metanicotine to protect alpha3beta4 nAChR function from long-term inhibition by antagonists or mixed agonists-antagonists was not previously recognized in the scientific literature, and would not have been expected based upon the activities of metanicotine and the other compounds, individually.

As indicated in paragraph 0014 of the subject patent application, metanicotine's surprising ability to protect nAChR from the inhibitory after-effects of other potentially therapeutic compounds is of great clinical significance. For example, metanicotine can be co-administered with other potentially therapeutic mixed agonists-antagonists that may otherwise be disqualified for therapeutic use due to their inhibitory side effects. Most of the pharmacological effects that could potentially be avoided are those associated with blocking predominant tone of either the sympathetic or parasympathetic nervous system. The alpha3beta4 nAChR is important in both of these systems. Examples of such side effects include, but are not limited to, vasoconstriction, constipation, pupil dilation, xerostemia (dry mouth), loss of accommodation (focusing ability), urine hesitancy and retention, impotence, anorexia, eructation (belching), and orthostatic hypotension. Thus, co-administration of metanicotine with other compounds can provide a means to tune a spectrum of effects to enhance receptor subtype-selective activation, thereby providing a more positive profile of effects.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: 
Roger L. Papke, Ph.D.

Date: June 16, 2004

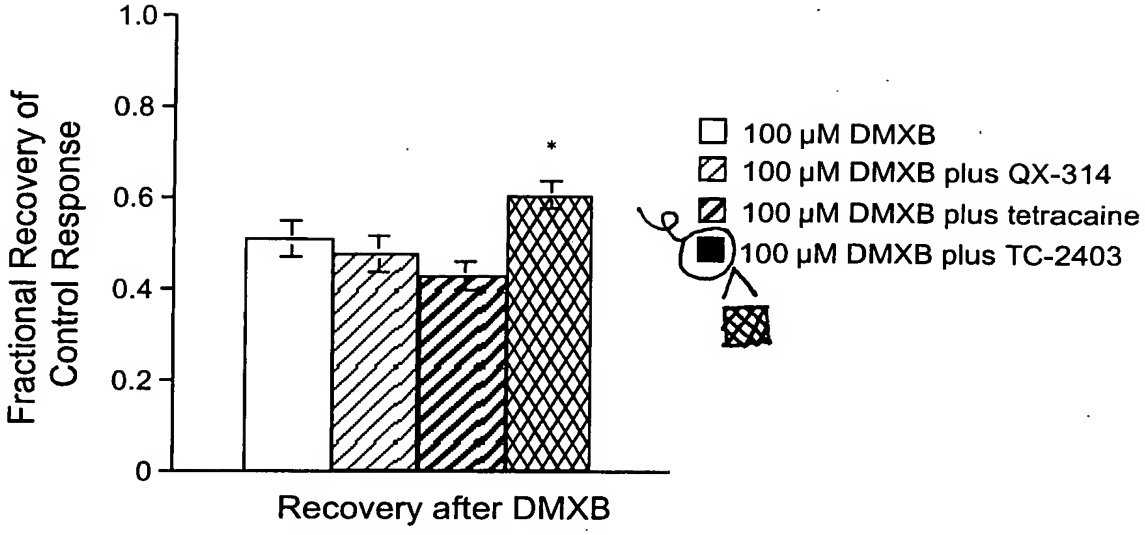

FIG. 6A

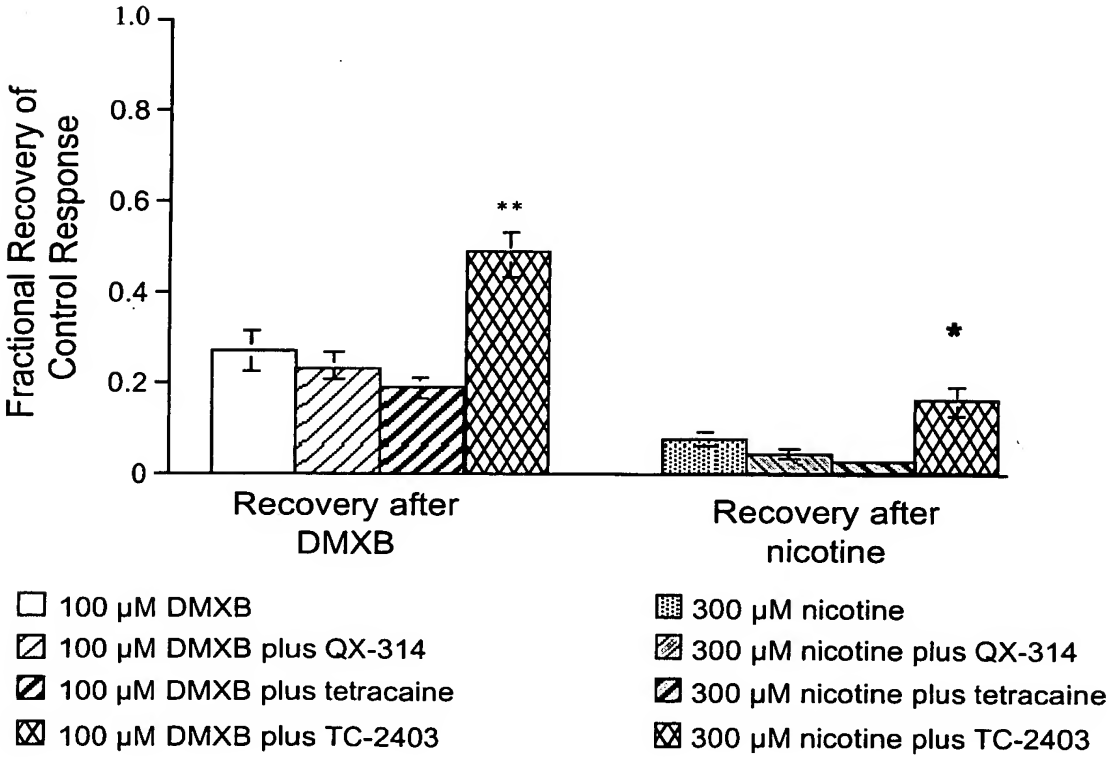

FIG. 6B